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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHERNYSHEV, OLGA N	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 09/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/826,290	DURHAM ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-74* is/are pending in the application.

4a) Of the above claim(s) *56-58 and 68-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-67 and 72-74* is/are rejected.

7)☒ Claim(s) *73* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 14, 2004 has been entered.

Response to Amendment

2. Claims 59 and 63 have been amended and claim 74 has been added as requested in the amendment of Paper filed on January 02, 2004.

Claims 56-74 are pending in the instant application.

Claims 56-58 and 68-71 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to invention nonelected by original presentation, there being no allowable generic or linking claim. See reasons of record in section 2 of Paper No. 15.

Claims 59-67 and 72-74 are under examination in the instant office action.

3. The Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

5. Applicant's arguments filed on January 02, 2004 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Objections

6. Claim 73 is objected to for being dependent from non-elected claim 68.

Claim Rejections - 35 USC § 112

7. Claims 59-67 and 72-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record in section 5 of Paper No. 15 and in section 8 of Paper mailed on July 03, 2003.

Applicant traverses the rejection on the premises that "the data presented in Table 1 represents the results from 148 subjects having Alzheimer's disease, 60 family members of these Alzheimer's disease subjects, and 32 unrelated controls" and, further, that "[t]he results of these experiments identified the statistically significant correlation between the level of API-6 and the presence of Alzheimer's disease in a subject" (middle at page 12 of the Response). Applicant further argues that the instant specification provides enough guidance on how to detect API-6 in any biological sample in subjects with Alzheimer's as compared to control (first paragraph at page 13 of the Response). These arguments have been fully considered but are not deemed persuasive for reasons that follow.

The instant specification, as filed, describes that AF-21 (as in AFs, Alzheimer's Disease-Associated Features), which corresponds to API (Alzheimer's Disease-Associated Protein Isoform)-6, as well as to SEQ ID NO: 36, 37, 38 and 39 (Table IV), is found to be 1.30 fold decreased in CSF samples of subjects having Alzheimer's disease as compared to normal

controls. One skilled in the art readily understands that a proper marker for a pathological condition must be present at significantly different levels in that pathological condition as compared to normal control and to other related diseases. Thus, in order to practice the claimed method and diagnose Alzheimer's disease by measuring the level of API-6 in a biological sample, a skilled practitioner would have to be able to distinguish between Alzheimer's disease patients, non-affected individuals and patients suffering from other neurological conditions not related to Alzheimer's disease. However, the instant specification fails to provide enough guidance necessary to practice the instant invention without undue experimentation. There is no information presented with regard to the levels of API-6 in CSF samples of patients suffering from any related neurodegenerative disorder, other than AD. There is also no data disclosed for levels of API-6 in any other biological sample additional to CSF. The Examiner maintains the position that the instant specification, as filed, fails to provide any evidence or sound scientific reasoning that would support a conclusion that finding of 1.3 fold decrease of API-6 in CSF samples of patients with Alzheimer's disease as compared to control values, can be predictive of diagnosis of AD using any biological samples other than CSF, or that any decrease in API-6 level in general is diagnostic of AD (as recited in claims 59-67 and 72, for example).

The instant invention relates to the filed of diagnosis of Alzheimer's disease (AD). According to the knowledge in the art, the Alzheimer's disease can be definitively diagnosed only by direct brain biopsy (see Clark et al., page 1164, for example). Therefore, one skilled in art would reasonably conclude that, in view of the absence of specific information regarding methods of diagnosis of the subjects participating in the study, patients identified in the instant specification as "148 subjects having Alzheimer's disease" most probably represent subjects

diagnosed with dementia of Alzheimer's type, which is not a conclusive diagnosis of AD, absent evidence to the contrary. Accordingly, it appears that in order to practice Applicant's invention, a skilled artisan would have to experiment to determine if API-6 is associated with confirmed cases of AD, what is the critical level of decrease in API-6 values that is indicative of AD, as well as what other biological samples contain API-6, and if API-6 values are also decreased in other biological samples of subjects with AD.

There is no disagreement that skill in the art is high enough for an artisan to be able to perform binding assay using any biological sample and detect API-6. However, such detection alone would not lead to diagnosis of AD for those reasons of record fully explained earlier in the instant office action, as well as in the previous communications of record. The standard of an enabling disclosure is not the ability to make and test if the invention worked but one of the ability to make and use with a reasonable expectation of success. In view of the lack of teachings and unpredictability of the art set forth earlier, and also the total absence of the working examples describing definitive diagnosis of AD in an individual, the instant specification is not found to be enabling for a method of diagnosing Alzheimer's disease. It would require undue experimentation and making a substantial inventive contribution for the skilled artisan to discover how to use Applicants' invention as currently claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 59-67, 72 and 74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 59 is vague and indefinite for recitation "detecting [...] API-6", followed by recitation "decreased level of API-6". The term "detection" generally refers to determination or discovery of the presence and is not equal to measurement. Therefore, there appears to be lack of antecedent basis within the claim for "decreased level" without previous reference to the act of measuring or determination of the level, amount, quantity or any other measurable unit, which is, when decreased, diagnostic of AD.

10. Claim 60 is vague and indefinite for reasons of record as applied to claim 59 in section 9 of the instant office action. Claim 60 recites steps of detecting of API-6, which are limited to detection of binding; therefore, it is not clear how detection of binding by itself can further lead to detection of decreased level of API-6. Clarification is required.

11. Claims 61-67, 72 and 74 are indefinite fro being dependent from indefinite claims.

Conclusion

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ɜ 1.6(d)0. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (571) 273-0870. Official papers should NOT be faxed to (571) 273-0870.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Olga N. Chernyshev, Ph.D.

OLGA N. CHERNYSHEV, PH.D.
PATENT EXAMINER